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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	**PAPER NUMBER**
1636	32

DATE MAILED: 03/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/139,425	ESMON ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 07/15/03 has been acknowledged.

In view of the Appeal Brief filed on 07/15/03, PROSECUTION IS HEREBY REOPENED. New grounds of rejection *are* set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Claims 1, 7, 12-14 and 19 have been amended.

Claims 1-25 are pending and are examined in this office action.

*Applicants are required to follow Amendment Practice under revised **37 CFR §1.121**. The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306**.*

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 1, 4, 6-7, 9-10, 13-14, 18, 19, 21-23 and 25 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the same reasons of record as set forth in the office action mailed on 02/12/03.

The scope of the invention as claimed encompasses any and all types of agents that selectively bind to the endothelial protein C receptor (EPCR). At best the specification only teaches an anti-EPCR-antibody and protein C that binds to the EPCR (see spec. pages 4-6 sec. B). The specification further teaches that only activated protein C (APC) is transported to the nucleus of the endothelial cells in HUVEC cells in vitro (spec. page 14, example-5). Besides anti-EPCR antibody and activated protein C the specification as filed fails to disclose any other agent that selectively binds to the EPCR and selectively translocate to the nucleus of endothelial cells. Furthermore, the specification as filed only teaches biotinlayted-anti-EPCR antibody and poly-L-lysine conjugated anti-EPCR antibody. The specification fails to disclose all conjugates wherein the conjugation has been achieved by all chemical means, fusion proteins or conjugate formed by indirect binding by all positively charged polymers or chimeric antibodies (see spec. page 8, sec. D). In addition the specification fails to disclose any triplex forming oligonucleotide, ribozymes guide sequences for ribozymes and antisense nucleotide sequences and transcription factor related to any gene.

Response to arguments

The applicant argues that even though the specification only demonstrates reduction to practice with single embodiment (an antibody to EPCR), **other molecules** are known, and be made and could be used. The applicant argues that the specification describes the structure of claimed agent by providing examples of domains know to interact with the well characterized EPCR (thereby, implicitly illustrating the chemical properties, hydrogen bond acceptor and donor sites arranged specifically of the claimed

agents). The applicant further argues that *"these agents may be organic, inorganic, proteins or even nucleic acids; specific binding is achieved through complementary interactions." See response pages 10-11.* Discussing the basic structure of an antibody the applicant the applicant concluded that "*in order for the agent to be delivered to the nucleus of endothelial cells, hydrogen bond, donor sites, hydrogen bond acceptor sites and chemical side groups, have to be in correct spatial location, orientation and have correct charge*" see response page 12. The applicant further argues *"that it is no coincidence that the antibody/epitopes and the claimed compounds/substrate interaction and structure are defined using, same well known and understood term in the art complementary". The applicant argues that once a substrate structure is known complementry interactions lie in the core of producing a well-defined structure that is able to recognize and bind to the target (i.e. lock and key analogy).* The applicant further argues that the specification describes methods that can be used to determine translocation of molecules to nucleus. The applicant concluded that one ordinary skill in the art could readily ascertain, without undue experimentation that whether or not molecues are translocated to the nucleus of endothelial cells.

However, this is found NOT persuasive. The core issue here is "selectively delivering a molecule to the nucleus of endothelial cells of large vessels" and NOT a molecule that just binds to EPCR. Furthermore the scope of invention as claimed is not limited to an antibody for EPCR or activated protein C, but encompasses any and all organic or inorganic compounds, proteins or even nucleic acids wherein specific binding is achieved through complementary interactions.

The earlier office action clearly states that under the law possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).* In the

instant case the agent as claimed has been defined only by a statement of function that requires the binding to the endothelial protein C receptor (EPCR), which conveyed no distinguishing information about the identity of the claimed agent, such as its relevant structural or physical characteristics.

Similarly, chemical conjugates, fusion proteins or conjugate formed by indirect binding by all positively charged polymers or chimeric antibodies conveyed no distinguishing information about the identity of the claimed substances, such as its relevant structural or physical characteristics. Furthermore the specification fails to disclose crystal structure of the EPC-Receptor, which one skill in the art can use to identify agents (key) that would bind to the EPC-receptor (lock). Therefore analogy to a "lock and key" is irrelevant in current context, since the structural components of the lock "the EPCR" are not known. In addition it would require extensive and undue amount of experimentation to identify a proper key (EPCR binding agent that homes to nucleus), since not all the binding agents would selectively deliver a molecule of interest to the nucleus of endothelial cells of large vessels. This is clearly evident from applicant's own disclosure, which teaches that protein C (a natural ligand for EPCR) does not migrate to the nucleus after binding to the EPCR (see specification page 14 example-5 (*emphasis added*). Similarly, triplex forming oligonucleotide, ribozymes guide sequences for ribozymes and antisense nucleotide sequences and transcription factor related to any and all genes conveyed no distinguishing information about the identity of the claimed molecules, such as its relevant structural or physical characteristics.

According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

Claims 1-25 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to

make and/or use the invention, for the same reasons of record as set forth in the office action mailed on 02/12/03.

Nature Of Invention:

The invention is drawn to selective delivery of a molecule to the nucleus of an endothelial cell of the large vessels through Endothelial Protein C Receptor (EPC-Receptor) using agents that selectively binds to the EPC-Receptor. The invention falls in the realm of protein and gene based therapeutics. Given the broadest reasonable interpretation the scope of invention as claimed encompasses a method exercised in-vivo (See also MPEP § 2111).

Breadth Of Claims And Guidance Provided By The Inventor:

The scope of invention as claimed encompasses the use of any and all agents that selectively binds to the EPC-Receptor and translocate to the nucleus of endothelial cells. Given the broadest reasonable interpretation the scope of the molecule to be delivered to cells encompasses a molecule with therapeutic or diagnostic characteristic (see spec. page 2, page 6 sec.C). In addition the scope of invention as claimed encompasses the delivery of the conjugates in-vivo via any and all routes of administration (local and systemic administration). The scope of invention as claimed encompasses the use of any and all conjugates wherein the conjugation has been achieved by all chemical conjugates, fusion proteins or conjugate formed by indirect binding by all positively charged polymers or chimeric antibodies. In addition the scope of invention as clamed encompasses the delivery of any and all triplex forming oligonucleotide, ribozymes guide sequences for ribozymes and antisense nucleotide sequences and transcription factor related to any gene.

At best the specification only teaches an anti-EPCR-antibody and protein C that binds to the EPCR (see spec. pages 4-6 sec. B). The specification further teaches that only activated protein C (APC) is transported to the nucleus of the endothelial cells in HUVEC cells in-vitro (spec. page 14, example-5). The specification discloses the selective delivery of streptavidin by using biotin labeled EPCR monoclonal antibodies (spec. page 13-14, example 3-4). In addition the specification only teaches poly-L-lysine conjugated anti-EPCR antibody. Besides anti-EPCR antibody and activated protein C

the specification as filed fails to disclose any other agent that selectively binds to the EPCR and selectively translocate to the nucleus of endothelial cells. In addition the specification as filed fails to disclose a single working example that teaches the delivery of the conjugates in-vivo via any and all routes of administration (systemic or local) that results in the delivery of the molecule to the nucleolus of the endothelial cells of any large blood vessel in a subject.

State Of Art And Predictability:

The state of the art at the time of filing teaches that Protein C functions as an anti coagulant when converted to active serine proteases from endothelial cell surface. Besides having affinity for Endothelial Protein C Receptor (EPCR) the Protein C also binds to the Thrombin-TM receptor complex in the endothelial micro-environment. Furthermore, the expression of Endothelial Protein C Receptor (EPCR) is not limited to endothelial cells of aorta but EPCR is also expressed in abundance in heart and placenta. In addition the EPCR expression has also been detected in lung, kidney and pancreas (see Fukudome et al, J Exp Med. 6;187(7):1029-35, 1998).

The art at the time of filing further teaches that the Gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy. (Rosenberg et al, Science 287:1751, 2000, Anderson WF, Nature 392:25-30, 1998; Verma et al Nature 389:239-242, 1997, Touchette, Nat. Med. 2(1) 7-8, 1996). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectations of current gene therapy protocols have been over sold without any apparent success (Touchette page 7, col.1 para. 2; page 8, col.2 para 1-4). The advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease. (Touchette, page 7, col.3, para.3). In instant case considering the scope of invention that encompasses in-vivo delivery the specification fails to disclose any particular use of triplex forming oligonucleotides, ribozymes and

antisense molecules. In addition the specification fails to disclose how one skilled in art would use any protein and/or diagnostic agent delivered into the nucleus of an endothelial cell. In addition, general systemic delivery of a complex that ends up in a pre-selected location in vivo is one of the most difficult obstacles to overcome. The infused particles binds to many cells they encounter in circulation and therefor would be diluted out before reaching their targets (see Anderson WF, page 25 col.2, para.4).

Response to arguments

The applicant argues that the invention is the discovery that molecules, which are bound by the EPCR on cells are taken up by the cell and can thereby be transported into nucleus. *The applicant admits that, "this is demonstrated in the application with respect to one molecule, an antibody to the receptor"* (see response. Page 7 para. 3 lines 2-3). However, the applicant argues that there is no evidence that such data is not predictive of efficacy for "other molecules" which could bind to the EPCR. The applicant argues that office must provide some evidence for why one skilled in the art would not think it was not enabled. The applicant argues that office fails to provide any evidence that results obtained from an antibody for receptor would not be predictive of other molecules. The applicant argues that the legal standard for the enablement issue is whether one skill in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. The applicant argues that Baumgartner demonstrated therapeutic intramuscular gene transfer to endothelial cells in need of treatment using a plasmid DNA. Therefore Baumgartner explicitly teaches successful gene therapy for endothelial cells. The applicant argues that Baumgartner directly refutes the examiner's assertion that gene therapy is highly unpredictable. The applicant argues that as stated on pages 9-10 of the specification, delivery is enhanced in the area of inflammation or coagulation process. The applicant argues that the composition may be delivered to a cell in-vitro, which can remain in culture or be returned to an individual. The applicant concluded that invention as claimed can be exercised without undue experimentation.

However, this is found NOT persuasive. The scope of invention as claimed encompasses selectively delivering a molecule of interest in to the nucleus of

endothelial cells of large vessels in-vivo via any and all routes of administration, wherein the molecule is conjugated to an agent that binds and transfer to the nucleus of the cell.

At best the specification only teaches an anti-EPCR-antibody and protein C that binds to the EPCR (see spec. pages 4-6 sec. B). The specification further teaches that only activated protein C (APC) is transported to the nucleus of the endothelial cells in HUVEC cells in-vitro (spec. page 14, example-5). The evidence that such data is not predictive of efficacy for "other molecules" which could bind to the EPCR could be best found in applicant's own disclosure where it clearly teaches that "**APC (*activated protein C*) but not the protein C, is transported to the nucleus of endothelial cells by EPCR**" see specification page 14 example-5 (*emphasis added*). Therefore it is even clear from the data presented in the specification that not all molecules that bind to EPCR are capable of delivering the molecule of interest into the nucleus of endothelial cells of large vessels (see Spec. Fig-3). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when disclosure is limited to few operative embodiments. Therefore, enablement issues are raised and discussed based on the state of the art at the time the invention was filed, skepticism raised in the enablement rejections are those raised one skill in the art.

Furthermore the scope of invention as claimed encompasses selective delivery of a molecule to the nucleus of an endothelial cell of the large vessels (in-vivo) through EPCR using any and all agents that selectively binds to the EPCR. The earlier office action clearly provided an evidence that the delivery of molecules to the nucleus of endothelial cells of large vessels in-vivo via any route of administration would be highly unpredictable, since EPCR is not only expressed in large blood vessels but also expressed on heart and placental tissuse. In addition the Protein C also binds to the Thrombin-TM receptor complex in the endothelial micro-environment. Therefore the systemic delivery of the conjugate would leads to the interaction with Thrombin-TM receptor complex and EPCR expressed on heart and placental tissue, thus making the conjugate immobilized before reaching to the EPCR expressed on the targeted large blood vessels. The specification fails to provide a single working example, which establishes that systemic or local (catherization) delivery of any agent that binds EPCR

resulted in the transportation of any molecule (drug, DNA, antibody, label etc) into the nucleus of endothelial of large vessels in any shapes and form.

Applicant cited Baumgartner et al (Circulation 97:1114, 1998) Lode et al (PNAS 95:2475, 1998), Nguyen et al (Cancer Gene Ther. 1997) Watanabe (Nippon Rinsho 53(3):724, 1998) and Feero et al (Gene Ther. 4(7):664-674, 1997) in support that invention as claimed in the instant application is fully enabled. However, this is found NOT persuasive because applicant's argument alone cannot take place of evidence lacking in the record (see In re Scarbrough 182 USPQ, (CCPA) 1979). The applicant fails to consider the inherent problem of transducing endothelial cells of a large blood vessel, which is subjected to a continuous flow of blood in vivo. In addition the infused particles binds to many cells (i.e. heart muscle cells, or cells expressing Thrombin-TM receptor) they encounter in circulation and therefor would be diluted out before reaching their targets.

At best Baumgartner et al teaches intra-muscular injection of a naked plasmid construct see page 1115, col.1). Lode teaches subcutaneous vaccination with transduced cells in a murine neuroblastoma model. Nguyen teaches gene delivery into malignant cells in vivo by conjugated adenovirus/DNA complex by direct injection in tumors. Watanabe teaches delivery of DNA molecules via transferrin receptor in tumor cells ex-vivo. Feero teaches transduction of myogenic cells by incorporation of transferrin into poly-L-lysine condensed DNA complex. None of the above mentioned references disclosed the subject matter of applicant's invention, which encompasses selective delivery of a molecule to the nucleus of an endothelial cell of the large vessels through EPCR using any and all agents that selectively binds to the EPCR. The references cited by the applicant do not recapitulate the unpredictability involved in the delivery of a molecule by an EPCR binding agent, especially in context with selective targeting of endothelial cells of large vessel in-vivo.

It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson , 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "**a patent is not a hunting license. It***

is not a reward for the search, but compensation for its successful conclusion") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, **reasonable detail must be provided in order to enable members of the public to understand and carry out the invention**. In instant case the applicant fails to disclose all agents (other than anti-EPCR-antibody and activated Protein C) that selectively binds to the EPCR. The specification fails to disclose any and all conjugates wherein the conjugation has been achieved by any all methods of chemical conjugation, fusion proteins or conjugate formed by indirect binding by all positively charged polymers or chimeric antibodies. In addition the specification fails to disclose any triplex forming oligonucleotide, ribozymes guide sequences for ribozymes and antisense nucleotide sequences and transcription factor related to any gene. For example, the specification fails to provide any guidance regarding what portion of an RNA molecule would be accessible in-vivo, since effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside the cells. In addition, the efficacy of antisense therapy is further compounded by the fact that base compositions as well as the secondary and tertiary structure of the target nucleotide sequence determines the accessibility of the sequence to an antisense sequence (see Branch TIBS, 23 Feb, 45-50, 1998).

Furthermore, selectively delivering molecules to the nucleus of endothelial cells of a large blood vessel is not considered routine in the art, and without sufficient guidance to a specific therapeutic molecule the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Claim Rejections - 35 USC § 102

Claims 13, 15, 20 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Foster et al (US 5225537, 1993) for the same reasons of record as set forth in the office action mailed on 9/11/02.

Foster teaches construction of a PAP-C fusion protein by using site directed mutagenesis to fuse PAP-I coding sequence with Protein C DNA. PAP-I is an anticoagulant protein (Col.17, example 3-4). The cited art further teaches a hybrid activated protein C comprising at least one lipocortin phospholipid-binding domain joined to a gla-domainless activated protein C (col22 line 11-23). The cited art teaches the coupling of protein C and activated protein C to PAP and lipocortin domains at molecular level. Given the broadest reasonable interpretation the cited art clearly anticipates the fusion protein coupling means as claimed (see MPEP 2111).

Response to arguments

The applicant argues that there is no indication in Foster that one should deliver a hybrid phospholipid-binding protein to large vessel *(response, page 16)*.

However, this is found NOT persuasive because preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. *See In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951)*. In instant case the cited art clearly teaches making of the PAP-C fusion protein by using site directed mutagenesis to fuse PAP-I coding sequence with Protein C DNA. The applicant argument that there is no indication in Foster that one should deliver a hybrid phospholipid-binding protein to large vessel has been found moot, since the structural limitations are able to stand alone in view of intended use of the product. In addition, if the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative

difference as compared to the prior art. *See In re Casey, 152 USPQ 235 (CCPA 1967) and In re Otto, 136 USPQ 458, 459 (CCPA 1963).* Thus the cited art clearly teaches the invention as claimed.

Claims 13, 15, 20 and 22-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Eibl et al (US 5571786, 1996) for the same reasons of record as set forth in the office action mailed on 9/11/02.

Eibl teaches a conjugate wherein the Activated Protein C is attached to thrombin coupled to CNBr-Sepharose 4B (col.6, example-3). The cited art teaches the attachment of a protein (thrombin) to activated protein C. The cited art further teaches the attachment of thrombin-activated protein C complex to a polymer (CNBr-Sepharose4B). Thus the cited art clearly anticipate the conjugate as claimed.

Response to arguments

The applicant argues that claim 13 is directed in part to a "fusion protein or conjugate formed by indirect binding by positively charged polymer, chimeric antibody or strepavidin. The cited art only teaches protein C mixed with thrombin gel an allowed to react and not to form conjugates (response page 16)

However, this is found NOT persuasive because invention as claimed is draw to a conjugate formed by indirect binding by a positively charged polymer". Eibl clearly teaches a conjugate wherein the Activated Protein C is attached to thrombin coupled to CNBr-Sepharose 4B (col.6, example-3). The thrombin-activated protein-C complex attached to CNBr-Sepharose4B clearly anticipate the conjugate as claimed.

Claims 13-15, 20 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Stearns-Kurosawa et al (PNAS 93:10212-10216, 1996).

The cited art teaches a Boitinlated-protein C preparation (page 10213, col.1 para.3). Thus the cited art clearly anticipated the invention as claimed in claims 13, 15, 20 and 22. Regarding claim 14 the cited art teaches isolation of anti-EPCR monoclonal

antibodies from mouse ascities using protein G column. The cited art further teaches a conjugate comprising anti-EPCR monoclonal antibodies conjugated with fluorescein-labeled anti-mouse IgG. Given the broadest reasonable interpretation to term - **diagnostic**[1] (*Serving to identify a particular disease; characteristic), the* fluorescein-labeled anti-mouse IgG is not a diagnostic agent since it has not used to identify a disease characteristic. Thus the cited art clearly teaches the antibody to EPCR attached to another molecule (see claim 14). Thus the invention as claimed is clearly anticipated by the cited prior art of record.

Response to arguments

The applicant argues that the cited art teaches a diagnostic agent that has been excluded from the claimed subject matter, therefore the cited art can not disclose the subject of claim 14. The applicant argues that mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency. In relying on the theory of inherency the office must provide a reasoning to support that alleged characteristic flow from the teaching of applied reference.

However, this is found NOT persuasive because preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. *See In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).* In instant case the cited art teaches isolation of anti-EPCR monoclonal antibodies from mouse ascities using protein G column. Therefore coupling of anti-EPCR monoclonal antibodies to G-protein claimed clearly anticipate the invention as claimed. In addition the recitation of claim limitation "not a diagnostic label" merely recites the purpose of a process or the intended use of a structure. The cited art clearly teaches conjugate comprising anti-

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EPCR monoclonal antibodies and a fluorescein-labeled anti-mouse IgG. Even though the anti-mouse IgG has been attached to a fluorescein-labeled, the diagnostic use of such a label only depend upon the detection of fluorescein-activity under permissive conditions (i.e flow cytometery). The anti-EPCR monoclonal antibody conjugated to anti-mouse IgG, clearly read upon a conjugate comprising an anti-EPCR antibody and a molecule to be delivered to a large vessel endothelial cell. In addition, if the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. *See In re Casey, 152 USPQ 235 (CCPA 1967) and In re Otto, 136 USPQ 458, 459 (CCPA 1963).* In instant case anti-EPCR monoclonal antibody when conjugated to anti-mouse IgG would certainly deliver the complex to the nucleus of an endothelial cell in-vitro. Thus the cited art clearly teaches the invention as claimed. Thus the cited art clearly teaches the antibody to EPCR attached to another molecule.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 571-272-0781.

The fax phone number for the organization where this application or proceeding is assigned is **703-872-9306**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sumesh Kaushal.
Examiner Art Unit 1636

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